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DOI:
10.1136/bmj.i2721

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Aronson, JK & Ferner, RE 2016, 'How similar are biosimilars?', *British Medical Journal*, vol. 353, pp. i2721. https://doi.org/10.1136/bmj.i2721

BMJ 2016;353:i2721 doi: 10.1136/bmj.i2721 (Published 17 May 2016)

EDITORIALS

How similar are biosimilars?

They are likely to be cost effective

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The United Kingdom has lagged behind other European countries in adopting biosimilars, said a recent article in the *Financial Times*,[1] and a British Biosimilars Association has been launched "to promote medicines that could shave a third off NHS prices."[2] The UK's chief pharmaceutical officer was quoted as saying that "biosimilar medicines have enormous potential to deliver increased patient access, as well as savings to the NHS, which can be reinvested elsewhere."[2]

Biological products ("biologics") include vaccines, blood and blood components, somatic cells, tissues (such as corneas, skin, and spermatozoa), and recombinant proteins.[3] They can be composed of sugars (such as heparin), proteins (monoclonal antibodies), nucleic acids (antisense oligonucleotides), or combinations of these (fusion proteins), but their precise structures are often not easily characterised.

Not like generics

Biosimilars are defined as biologics that are similar to other biologics already authorised for use.[4] When biosimilar proteins are synthesised, the primary amino acid sequence is likely to be preserved, but there can be differences in glycosylation, deamination, or oxidation and in the three dimensional structure, which can affect the interaction of the protein with other molecules. Because of such differences the World Health Organization introduced a nomenclature that involved qualifying with Greek letters the names of some compounds made recombinantly by different manufacturers: follitropin alfa, beta, and gamma and epoetin alfa, beta, theta, and zeta are examples.[5] One highly glycosylated epoetin was given a different name altogether, darbepoetin.

Biosimilars should not be regarded as generic equivalents of originator medicinal products, because they are complex molecules, expected to differ more from the originator molecules than generic versions of non-biologics. One cannot be sure that two biosimilars will have similar benefits and harms. Head to head comparisons of biosimilars are infrequent, and indirect comparisons may be inadequate. For example, in a network meta-analysis of the effects of biosimilars of epoetin the authors reported that the comparative benefits and harms of the different compounds were very uncertain.[6]

Nevertheless, regulators and market authorisation holders generally take considerable care to ensure that biosimilars are (as the European Medicines Agency states) "highly similar to the reference medicinal product in physicochemical and biological terms,"[7] under principles laid down by the International Conference on Harmonization,[8] the EMA,[8] and the US Food and Drug Administration.[9] These include, for example, demonstrably similar pharmacokinetic and pharmacodynamic properties and being used in the same dosage as the originator product. The UK National Institute for Health and Care Excellence (NICE) has provisions for recommending biosimilars when appropriate.[10]

Prescribing cheaper biosimilars might save the NHS an estimated 10% of the cost of the relevant biologics, a probable worthwhile saving, as biologics are often very expensive. For example, the NHS spent over £140m (€178m; $200m) on the tumour necrosis factor alfa inhibitor infliximab in 2013-14, some 15 years after it was first marketed as Remicade; NICE has since recommended the use of two infliximab biosimilars, Remsima and Inflectra,[11-13] both of which have been thoroughly evaluated. They are identical to the originator product in pharmaceutical form, strength, composition, and route of administration. The physicochemical and biological characters, possible contaminants and impurities, and stability of Remsima have been reported.[14] Comparison of its biological actions with those of the originator product showed only minor differences in relative binding affinities for the FcγRIIIa receptor subtype, for example, and these seemed to be biologically insignificant. The pharmacokinetics were almost identical, and clinical markers of disease activity responded equally well to the reference and biosimilar products in patients with rheumatoid arthritis or ankylosing spondylitis. Finally, in a 54 week comparative study the two products were therapeutically equivalent when combined with methotrexate in patients with rheumatoid arthritis.

When evidence of this kind is available, there should not be undue concern over starting treatment with a biosimilar rather than the originator drug, although switching between products might not be straightforward.

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Naming problems

Naming and prescribing biosimilars also create problems. An estimated 30 biologics, with combined sales of $51bn (£35bn; €45bn), came off patent in 2015,[15] opening the door to biosimilars. The task of naming them has therefore become crucial, and countries have adopted different methods. WHO has proposed a voluntary scheme in which most biologics would be given a "biological qualifier," a random four letter code and an optional two digit check sum, tied to the place of manufacture. However, the system is highly controversial, partly because the codes are meaningless.[16 17]

In the meantime, the advice on prescribing biosimilars is to use the brand name of your preferred product. After treatment has begun, the same product should continue to be used, if possible, because of potential small differences between biosimilars, which cannot be considered to be completely interchangeable.[18]

Competing interests: We have read and understood BMJ policy on declaration of interests and declare: JKA is a member of a NICE technology appraisal committee, a member of the Advisory Board of the British National Formularies, and a president emeritus of the British Pharmacological Society; however, the opinions stated in this article are his own and do not necessarily reflect the views of those organisations or of anyone associated with them. REF is NHS member of NICE's Appeal Panel, and his unit receives funding from MHRA; however, the opinions stated in this article are his own and do not necessarily reflect the views of those organisations or of anyone associated with them. Both authors have from time to time prepared medicolegal reports relating to licensed and unlicensed products. Neither has any financial or other interests in any company that manufactures the medicinal products discussed, licensed or unlicensed.

Provenance and peer review: Commissioned; not externally peer reviewed.

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